Precision Medicine in Type 2 Diabetes

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Precision medicine in Type 2 diabetes: Clinical markers of insulin resistance are associated with altered short and long-term glycemic response to DPP4-inhibitor therapy

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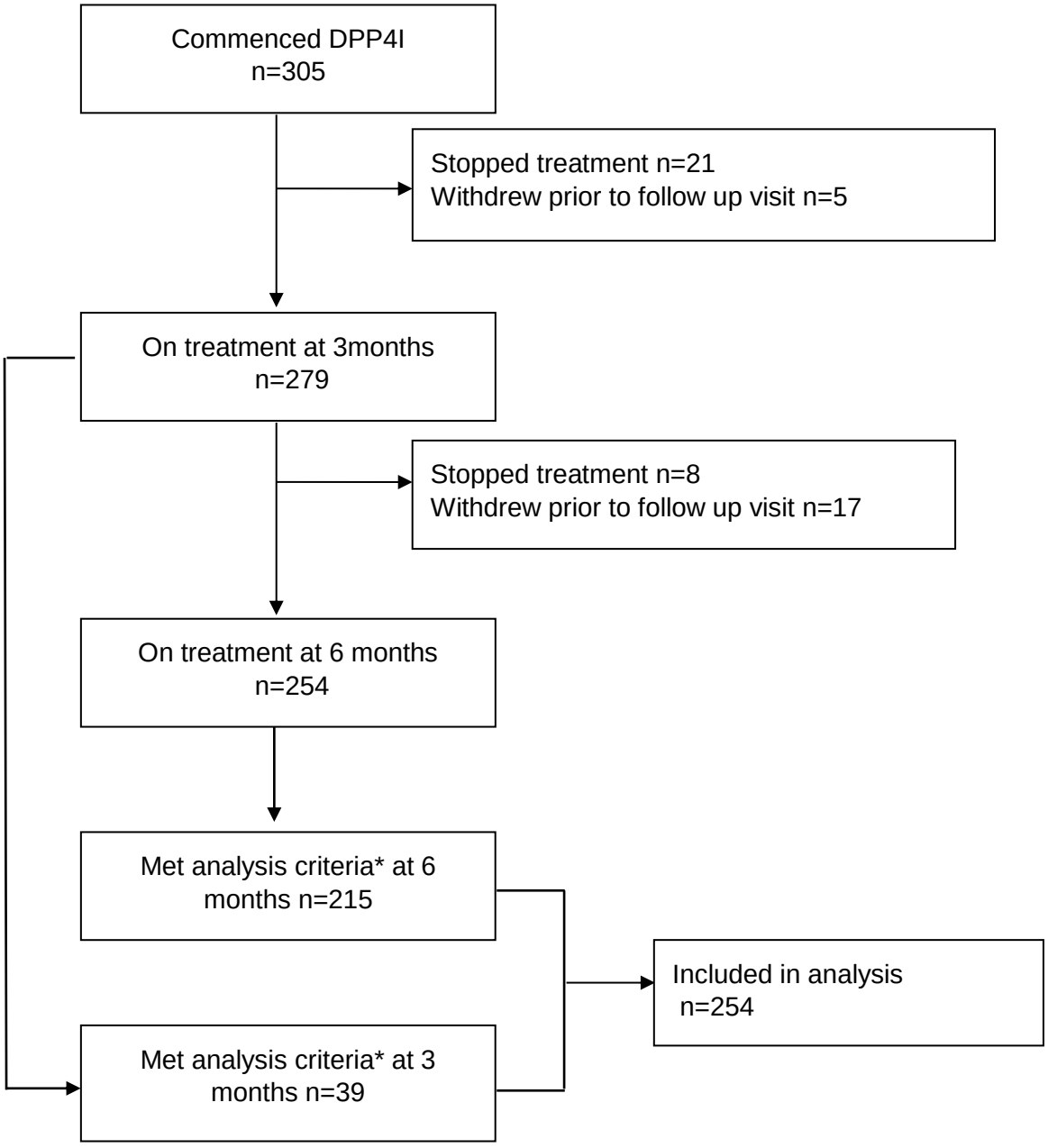
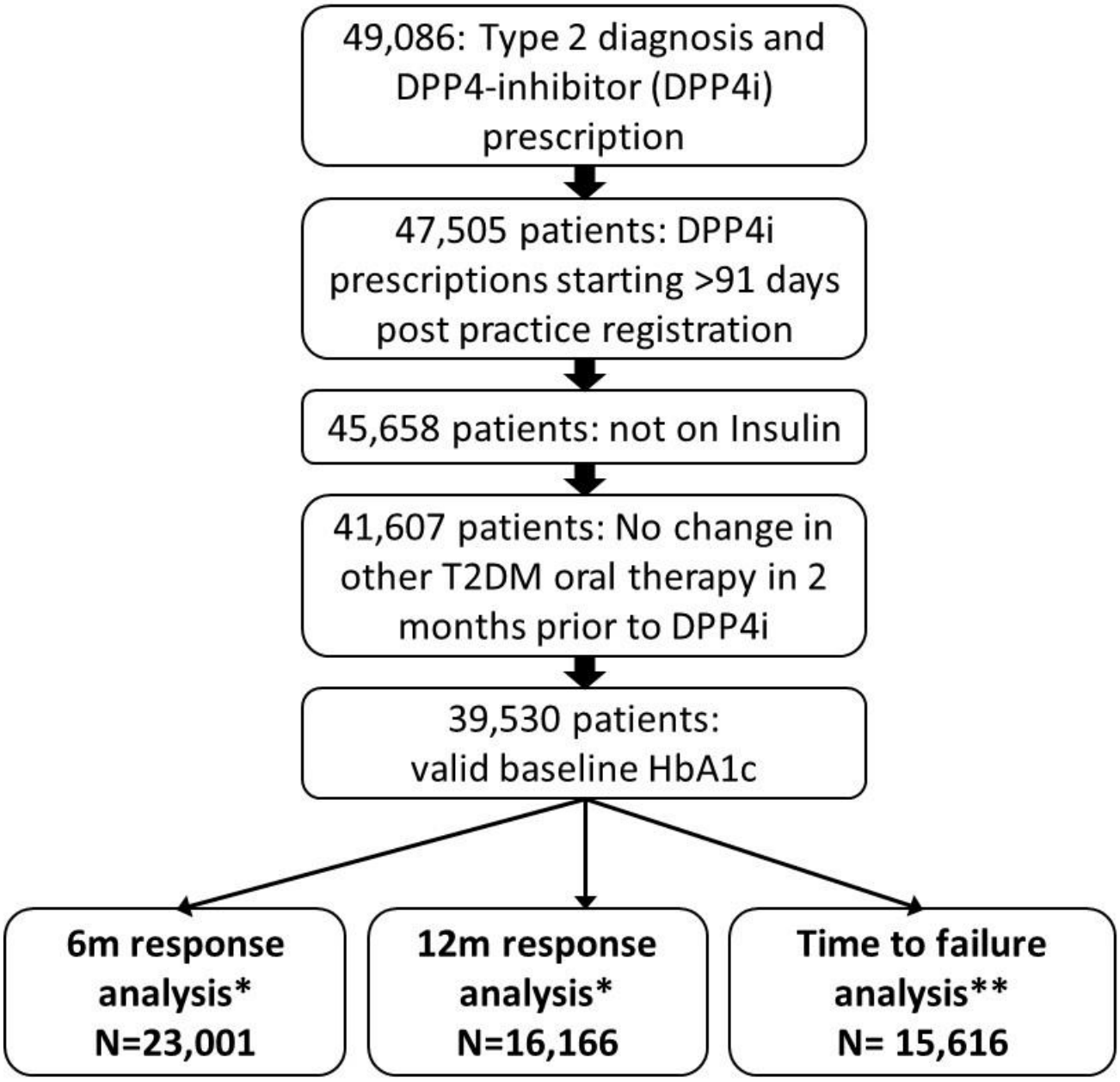
Supplementary figure 1a: PRIBA study Profile

*Analysis inclusion criteria: no additional of non DPP4 glucose lowering therapy, or discontinuation of >1 co-therapy, between baseline and follow up HbA1c. Self-reported DPP4 adherence (over 2 weeks prior to HbA1c) ≥75%. Participant not receiving insulin treatment at study baseline.



Supplementary Figure 1b: CPRD study profile



*No change in co-therapy over period of interest

**Additional inclusion criteria: baseline HbA1c 7-11%, remained on DPP4i therapy for at least 3m

Supplementary table 1: Associations between markers of insulin resistance and HbA1c response after 6 months, overall (Data table for Figure 1) and stratified by sex in a) PRIBA and b) CPRD. Beta coefficient represents the change in HbA1c per standard deviation higher predictor level, a positive coefficient represents an association with reduced response.

a) PRIBA

	All participants			Males (64%)		Females (36%)	
	Number with valid baseline data	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI)	p-value
HOMA-IR*	242	2.17 (0.62 to 3.72)	0.01	1.69 (-0.26 to 3.64)	0.09	2.87 (0.22 to 5.52)	0.03
Fasting C-peptide	251	1.67 (0.17 to 3.17)	0.03	1.44 (-0.49 to 3.36)	0.14	1.91 (-0.56 to 4.39)	0.13
UCPCR**	203	1.65 (-0.07 to 3.37)	0.06	3.35 (1.05 to 5.65)	<0.01	-0.56 (-3.16 to 2.04)	0.67
Fasting Triglycerides	240	2.54 (0.99 to 4.08)	<0.01	2.20 (0.35 to 4.05)	0.02	3.31 (0.33 to 6.29)	0.03
BMI	254	0.96 (-0.54 to 2.46)	0.21	1.23 (-0.89 to 3.35)	0.25	0.29 (-1.98 to 2.56)	0.80
HDL	243	0.20 (-1.36 to 1.75)	0.81	0.56 (-1.1 to 2.62)	0.60	-0.95 (-3.60 to 1.70)	0.48
SHBG***	214	-1.19 (-2.81 to 0.42)	0.15	-1.19 (-3.35 to 0.97)	0.28	-1.23 (-3.79 to 1.33)	0.34

* HOMA2 measured insulin resistance **UCPCR = post meal urine C-peptide Creatinine ratio; ***SHBG = sex-hormone binding globulin

b) CPRD

	All patients			Males (61%)		Females (39%)	
	Number with valid baseline data	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI)	p-value
BMI	19,430	0.96 (0.78 to 1.15)	<0.01	1.04 (0.78 to 1.30)	<0.01	0.78 (0.51 to 1.05)	<0.01
Triglycerides	15,404	0.72 (0.50 to 0.93)	<0.01	0.82 (0.56 to 1.09)	<0.01	0.57 (0.21 to 0.95)	<0.01
HDL	17,058	-0.08 (-0.28 to 0.13)	0.46	-0.22 (-0.49 to 0.05)	0.11	-0.21 (-0.55 to 0.13)	0.22

Supplementary table 2: Effect sizes for insulin resistance markers controlling for routine clinical characteristics (baseline HBA1c, age at therapy, sex, duration of diabetes, eGFR, ethnicity (CPRD only: white, non-white, missing) and co-therapy change (PRIBA only, CPRD patients all on unchanged therapy). Beta coefficient represents the change in HbA1c at 6 months per standard deviation increase in the predictor, a positive coefficient represents an association with reduced response.

a) PRIBA

	Number of patients	Beta coefficient (95% CI)	p-value
HOMA-IR	205	2.57 (0.73 to 4.40)	<0.01
Fasting C-peptide	212	2.13 (0.33 to 3.94)	0.02
Fasting Triglycerides	215	2.34 (0.44 to 4.25)	0.02
BMI	215	0.67 (-1.15 to 2.50)	0.47
HDL-c	215	0.09 (-1.69 to 1.86)	0.92
SHBG	185	-1.04 (-3.00 to 0.91)	0.29

b) CPRD

	Number of patients	Beta coefficient (95% CI)	p-value
Triglycerides	13,089	0.67 (0.41 to 0.94)	<0.01
BMI	11,683	0.87 (0.61 to 1.12)	<0.01
HDL-c	13,187	-0.11 (-0.35 to 0.14)	0.40

Supplementary table 3: Associations between triglycerides and BMI and HbA1c response after 6 months adjusted for baseline HbA1c, fasting glucose and co-therapy change in PRIBA. Beta coefficient represents the change in HbA1c at 6 months per standard deviation increase in the predictor, a positive coefficient represents an association with reduced response.

	Number of patients	Beta coefficient (95% CI)	p-value
HOMA-IR*	242	1.76 (0.15 to 3.38)	0.03
Fasting C-peptide	242	1.71 (0.21 to 3.21)	0.03
UCPCR**	195	1.50 (-0.22 to 3.21)	0.09
Fasting Triglycerides	231	2.39 (0.84 to 3.94)	<0.01
BMI	244	1.10 (-0.41 to 2.61)	0.15
HDL-c	233	0.20 (-1.36 to 1.76)	0.80
SHBG***	206	-0.90 (-2.53 to 0.73)	0.28

* HOMA2 measured insulin resistance **UCPCR = post meal urine C-peptide Creatinine ratio;
***SHBG = sex-hormone binding globulin

Supplementary table 4: Associations between routine markers of insulin resistance and HbA1c response after 12 months in CPRD. For each predictor we ran a separate linear regression model, adjusted for baseline HbA1c. Beta coefficient represents the change in HbA1c at 12 months per standard deviation increase in the predictor, a positive coefficient represents an association with reduced response.

	Number of patients	Beta coefficient (95% CI)	p-value
Triglycerides	13,942	0.70 (0.45 to 0.96)	<0.01
BMI	11,206	0.81 (0.59 to 1.04)	<0.01
HDL-c	12,273	-0.32 (-0.57 to -0.08)	0.01

Supplementary table 5: Associations between triglycerides and BMI and HbA1c response after 6 months in a combined model adjusted for baseline HbA1c, and (PRIBA only) co-therapy change in a) PRIBA and b) CPRD. Beta coefficient represents the change in HbA1c at 6 months per standard deviation increase in the predictor, a positive coefficient represents an association with reduced response.

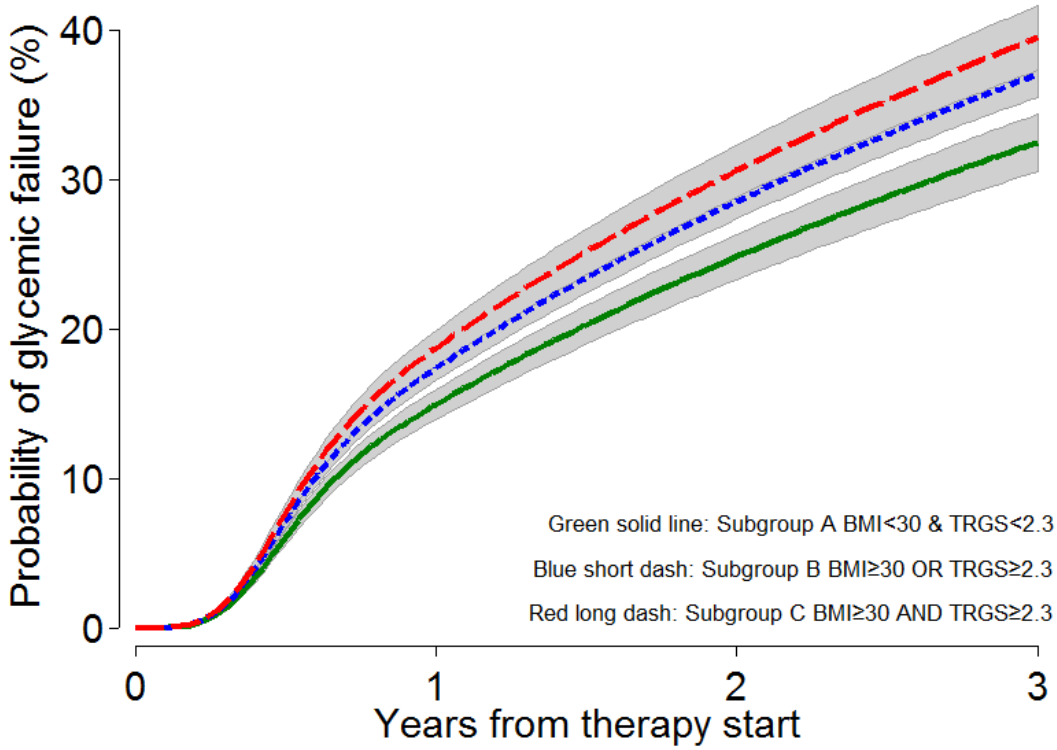
	a) PRIBA (n=240)		b) CPRD (n=13,543)	
	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI)	p-value
Triglycerides	2.33 (0.71 to 3.94)	<0.01	0.56 (0.32 to 0.79)	<0.01
BMI	0.44 (-1.17 to 2.04)	0.59	0.96 (0.73 to 1.18)	<0.01

Supplementary table 6: CPRD hazard ratios for time to glycaemic failure (confirmed HbA1c ≥69 mmol/mol (8.5%)) for each predictor in the multivariable survival model (n=15,616)

	Hazard ratio	95% CI	p-value
BMI & Triglyceride subgroup			
BMI<30 & TRGS<2.3	1 (reference)		
BMI≥30 OR TRGS≥2.3	1.17	1.08-1.27	<0.001
BMI≥30 & TRGS≥2.3	1.28	1.16-1.41	<0.001
Clinical characteristics			
Baseline HbA1c (mmol/mol)*	1.061	1.058-1.064	<0.001
Age at therapy start (year)*	0.990	0.986-0.994	<0.001
Duration of diabetes (year)*	1.004	0.997-1.011	0.29
Female vs male sex	1.075	0.999-1.152	0.04
eGFR (ml/min/1.3m^2)*	1.001	0.999-1.002	0.49

*For continuous variables the hazard ratio represents the change in hazard ratio for a 1 unit increase in the predictor. A hazard ratio > 1 indicates a higher value of that variable is associated with shorter durability of glycaemic response

Supplementary Figure 2: Probability of glycemic failure (confirmed HbA1c ≥8.5%) over 3 years in CPRD in subgroups defined by the presence or absence of obesity (BMI>=30 kg/m^2) and high triglycerides (TRGs >=2.3mmol/L) - *Subgroup A*: non-obese and normal triglycerides, *Subgroup B*: non-obese OR normal triglycerides, *Subgroup C*: obese and high triglycerides).



Supplementary table 7: CPRD hazard ratios by BMI & Triglyceride subgroup for time to glycaemic failure defined as

a) Confirmed HbA1c ≥53 (7.5%) (n=15,616)*

	Hazard ratio	95% CI	p-value
BMI & Triglyceride subgroup			
BMI<30 & TRGS<2.3	1 (reference)		
BMI≥30 OR TRGS≥2.3	1.08	1.02-1.14	0.01
BMI≥30 & TRGS≥2.3	1.17	1.09-1.25	<0.001

b) Confirmed return to baseline HbA1c level specific to each patient (n=15,616)*

	Hazard ratio	95% CI	p-value
BMI & Triglyceride subgroup			
BMI<30 & TRGS<2.3	1 (reference)		
BMI≥30 OR TRGS≥2.3	1.14	1.05-1.24	0.002
BMI≥30 & TRGS≥2.3	1.29	1.16-1.42	<0.001

*****adjusted for baseline HbA1c, age at therapy, duration of diabetes, sex and eGFR

GLP-1 receptor agonist comparison analysis

Supplementary table 8: GLP-1 receptor agonists - subject baseline characteristics

	PRIBA (n=339)	CPRD (n=4,464)
Characteristics mean (SD) unless stated		
Baseline HbA1c (mmol/mol)	83 (18)	79 (17)
Baseline HbA1c (%)	9.7 (1.7)	9.4 (1.6)
Age at therapy start (years)	55 (10)	59 (9)
Age at diagnosis (years)	47 (10)	51 (8)
Male sex (%)	56%	58%
Duration of diabetes (years)	8 (5)	8 (5)
BMI - median (IQR); mean(SD)	38 (35-44); 40 (8)	37 (34-42); 38 (7)
Ethnicity (%)		
White	95%	46%
Non-White	5%	3%
Missing	0%	51%
Biomarkers median (IQR); mean (SD) unless stated		
*=log-transformed		
Triglycerides (mmol/L)	1.9 (1.4-2.6); 2 (1.1)*	2.0 (1.4-2.8); 2.0 (0.5)*
HDL-c (mmol/L)	1.1 (0.9-1.2); 1.1 (0.3)*	1.1 (0.9-1.2); 1.1 (0.2)*
LDL-c (mmol/L)	2.2 (1.8-2.8); 2.2 (0.8)*	2.0 (1.6-2.6); 2.0 (0.4)*
SHBG (nmol/L)	23 (17-36); 24 (14)*	NA
Fasting C-peptide (pmol/L)	1310 (962-1700); 1255 (594)*	NA
HOMA2-%B	49 (32-75); 48 (29)*	NA
HOMA2 IR	4.1 (3.0-5.3); 4.0 (2.1)*	NA
UCPCR nmol/mmol	3.5 (1.9-6.0); 3.1 (2.8)*	NA
eGFR (ml/min/1.3m^2)	92 (77-111); 95 (27)	88 (74-102); 88 (22)
GAD or IA2 positive (%)	1%	NA
Therapy		
Number of concomitant therapies at therapy start (% of total)		
0	1%	2%
1	26%	36%
2	51%	54%
3+	22%	8%
GLP-1 type (% of total)		
Dulaglutide	0%	1%
Exenatide	40%	44%
Liraglutide	60%	50%
Lixisenatide	0%	6%

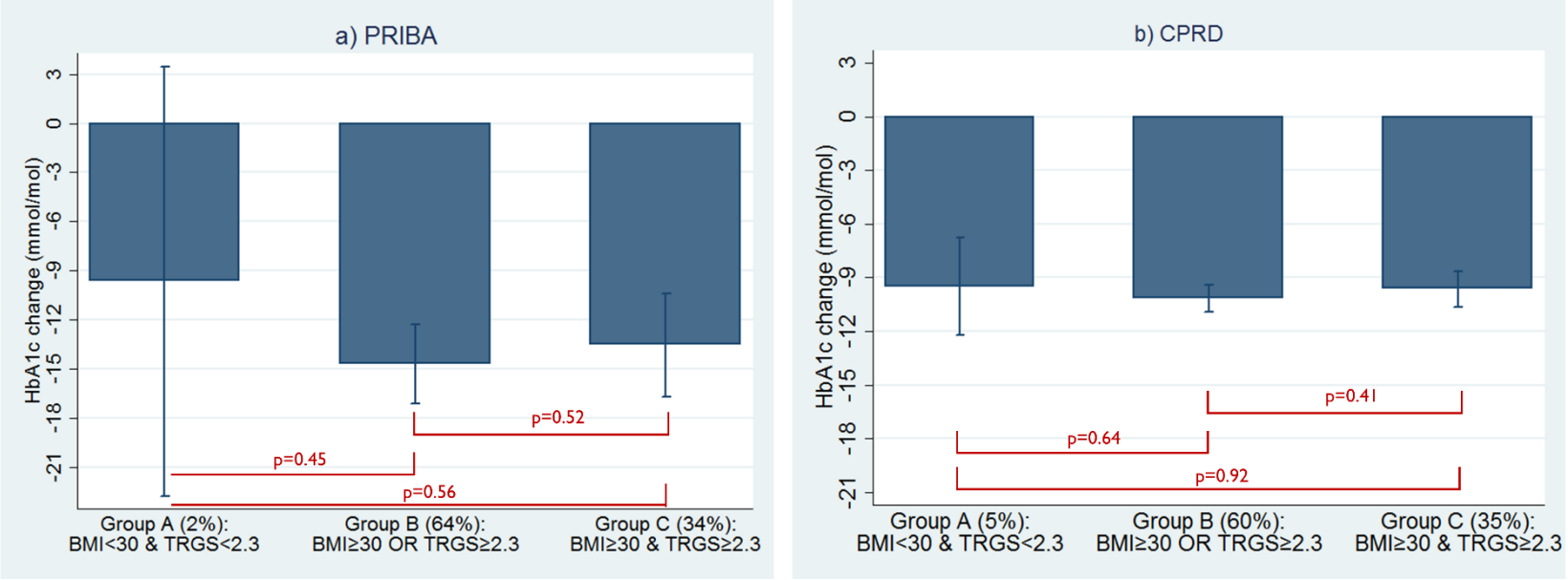
Supplementary table 9: GLP-1 receptor agonists - Associations between markers of insulin resistance and HbA1c response after 6 months, overall (Data table for Supplementary Figure 2) in a) PRIBA and b) CPRD. Beta coefficients represent the change in HbA1c per standard deviation higher predictor level, a positive coefficient represents an association with reduced response.

	PRIBA			CPRD		
	Number with valid baseline data	**Beta coefficient (95% CI)**	**p-value**	**Number with valid baseline data**	**Beta coefficient (95% CI)**	**p-value**
HOMA-IR*	300	0.73 (-0.99 to 2.44)	0.41	NA	NA	NA
Fasting C-peptide	333	0.24 (-1.38 to 1.85)	0.78	NA	NA	NA
UCPCR**	245	0.45 (-1.37 to 2.26)	0.63	NA	NA	NA
Triglycerides	316	0.07 (-1.59 to 1.73)	0.93	2,848	-0.07 (-0.65 to 0.49)	0.80
BMI	337	0.11 (-1.49 to 1.70)	0.90	4,016	-0.19 (-0.66 to 0.28)	0.43
HDL	315	1.08 (-0.55 to 2.71)	0.19	3,126	0.01 (-0.53 to 0.55)	0.97
SHBG***	317	0.56 (-1.09 to 2.21)	0.50	NA	NA	NA

Supplementary table 10: Mean (95% CI) 6 month baseline HbA_{1c} standardised glycemic response (mmol/mol) for DPP4-inhibitors and GLP receptor agonists in PRIBA and CPRD. Baseline HbA1c is standardised to the mean PRIBA baseline level of 74mmol/mol (8.9%) for all subgroups.

	DPP4-inhibitors		GLP-1 receptor agonists	
BMI & Triglyceride subgroup	**PRIBA**	**CPRD**	**PRIBA**	**CPRD**
BMI<30 & TRGS<2.3	-11.26 (-14.1 to -8.43)	-10.28 (-10.72 to -9.85)	-9.64 (-22.75 to 3.48)	-9.49 (-12.2 to -6.78)
BMI≥30 OR TRGS≥2.3	-9.94 (-12.24 to -7.64)	-8.79 (-9.12 to -8.47)	-14.7 (-17.11 to -12.29)	-10.16 (-10.91 to -9.4)
BMI≥30 & TRGS≥2.3	-5.23 (-8.62 to -1.84)	-7.47 (-7.95 to -6.99)	-13.54 (-16.69 to -10.39)	-9.64 (-10.65 to -8.63)

Supplementary Figure 3: GLP-1 receptor agonists - predicted mean absolute HbA1c change from baseline at 6 months in a) PRIBA b) CPRD across subgroups defined by the presence or absence of obesity (BMI>=30 kg/m^2) and high triglycerides (TRGs >=2.3mmol/L) - *Subgroup A*: non-obese and normal triglycerides, *Subgroup B*: non-obese OR normal triglycerides, *Subgroup C*: obese and high triglycerides. Baseline HbA1c is standardised to the mean PRIBA baseline level of 74mmol/mol (8.9%) for all subgroups. Error bars denote 95% confidence intervals.



Supplementary table 10: GLP-1 receptor agonists - CPRD hazard ratios for time to glycaemic failure (confirmed HbA1c ≥69 mmol/mol (8.5%) for each predictor in the multivariable survival model (n=2,795)

	Hazard ratio	95% CI	p-value
BMI*	1.01	1.00-1.02	0.29
Triglycerides*	0.99	0.95-1.04	0.80
Baseline HbA1c (mmol/mol)*	1.05	1.04-1.06	<0.001
Age at therapy start (year)*	0.98	0.97-0.99	<0.001
Duration of diabetes (year)*	1.01	0.99-1.03	0.21
Female vs male sex	0.78	0.67-0.91	0.001
eGFR (ml/min/1.3m^2)*	1.00	1.00-1.00	0.63

*For continuous variables the hazard ratio represents the change in hazard ratio for a 1 unit increase in the predictor. A hazard ratio > 1 indicates a higher value of that variable is associated with shorter durability of glycaemic response

Supplementary table 11: GLP-1 receptor agonists - CPRD hazard ratios for time to glycaemic failure (confirmed HbA1c ≥69 mmol/mol (8.5%)) for each predictor in the multivariable survival model (n=2,795)

	Hazard ratio	95% CI	p-value
BMI & Triglyceride subgroup			
BMI<30 & TRGS<2.3	1 (reference)		
BMI≥30 OR TRGS≥2.3	1.21	0.85-1.73	0.29
BMI≥30 & TRGS≥2.3	1.13	0.79-1.63	0.50
Clinical characteristics			
Baseline HbA1c (mmol/mol)*	1.05	1.04-1.06	<0.001
Age at therapy start (year)*	0.98	0.97-0.99	<0.001
Duration of diabetes (year)*	1.01	0.99-1.03	0.22
Female vs male sex	0.79	0.68-0.92	0.002
eGFR (ml/min/1.3m^2)*	1.00	1.00-1.00	0.60

*For continuous variables the hazard ratio represents the change in hazard ratio for a 1 unit increase in the predictor. A hazard ratio > 1 indicates a higher value of that variable is associated with shorter durability of glycaemic response

Supplementary Figure 4: GLP-1 receptor agonists - Probability of glycemic failure (confirmed HbA1c ≥8.5%) over 3 years in CPRD in subgroups defined by the presence or absence of obesity (BMI>=30 kg/m^2) and high triglycerides (TRGs >=2.3mmol/L) - *Subgroup A*: non-obese and normal triglycerides, *Subgroup B*: non-obese OR normal triglycerides, *Subgroup C*: obese and high triglycerides).